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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
JOHANNSEN, DIANA B	
ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/420,433	SIDRANSKY, DAVID	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7-12,14,18-22 and 24-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-12,14,18-22 and 24-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 25, 2008 has been entered.

Claims 1-4, 11-12, 18-22, and 25-26 have been amended. Claims 1-4, 12, 14, 18-22, and 24-26 remain pending and under consideration.

Election/Restrictions

2. Claims 2-3 and 7-11 as amended (as well as embodiments of claim 1 as amended) are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the claims have amended such that they appear to be directed to detection of non-mutant or non “neoplastic” forms of the group of target nucleic acids recited in the claims. Thus, the claims encompass detection of target sequences with different structural and functional properties than those under examination. Had these claims been originally presented they would have been restricted from the claims now under consideration, as the invention of claims 2-3 and 7-11 requires a different search and the consideration of a different group of prior art references. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original

presentation for prosecution on the merits. Accordingly, claims 2-3 and 7-11 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. However, it is noted that as claim 1 links the invention of claims 2-3 and 7-11 with that of claim 4 and the remainder of the claims, claim 1 has been further addressed below.

3. Claim 1 link(s) the invention now under consideration with that of claims 2-3 and 7-11. The restriction requirement between the linked inventions is **subject to** the nonallowance of the linking claim(s), claim 1. Upon the indication of allowability of the linking claim(s), the restriction requirement as to the linked inventions **shall** be withdrawn and any claim(s) depending from or otherwise requiring all the limitations of the allowable linking claim(s) will be rejoined and fully examined for patentability in accordance with 37 CFR 1.104 **Claims that require all the limitations of an allowable linking claim** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

Applicant(s) are advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, the allowable linking claim, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Claim Rejections - 35 USC § 112, first paragraph

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 1 has been amended such that it appears to be directed to non-mutant or non "neoplastic" versions of APC, DCC, NF1, NF2, RET, VHL, and/or WT1 nucleic acids. The originally filed specification does not disclose such nucleic acids. Rather, the specification states that "In its broadest sense, the present invention allows the detection of any neoplastic target nucleic acid sequence" and teaches that such neoplastic target nucleic acids encompass "mutant" nucleic acids (page 9). The specification goes on to state that "Numerous nucleic acids having mutant nucleotide sequences that produce an abnormal gene product are known to be associated with various neoplasias" and that "Among the most common mutant nucleotide sequences are those occurring in oncogenes and tumor suppressor genes" (page 9); the specification then proceeds to identify the genes of the claims as such sequences in Table 1. The genes of the claims are not otherwise referenced in the specification, and no version or variant of the genes other than this "mutant" version is ever disclosed.

Accordingly, because applicant's amendment broadens the claim to encompass a population of nucleic acids not originally disclosed, the amendment introduces new matter.

6. Claims 1, 4, 12, 14, 18-22, and 24-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) the breadth of the claims; (B) the nature of the invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the existence of working examples; and (H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (*MPEP* 2164.01(a)).

It is first noted that claim 1 encompasses the subject matter of claim 4, and thus embraces the elected invention. Claim 1 and 4 are drawn to methods in which a "target nucleic acid" selected from APC, DCC, NF1, NF2, RET, VHL, and WT-1 and including a mutation is detected in a tumor margin tissue specimen that is "external to a primary neoplasm" and "histologically normal upon examination." Claims 12 and 14 are drawn

to methods in which a "target nucleic acid having a mutation" that is selected from APC, DCC, NF1, NF2, RET, VHL, and WT-1 is detected in a surgical margin that is "histologically normal upon examination" as an indicator of metastases. Claim 18 encompasses detection of such a target nucleic acid in a "tissue specimen which is external to a primary neoplasm" and "histologically normal," while claim 19 requires the presence of such a nucleic acid in a "tumor margin tissue specimen" that "appears histologically normal." Claims 20-22 and 24 are drawn to methods in which a "target nucleic acid" selected from APC, DCC, NF1, NF2, RET, VHL, and WT-1 and including a mutation is detected in a "lymph node tissue specimen" that is "external to a primary neoplasm" and which "appears histologically normal." Claims 25-26 are drawn to methods in which a "target nucleic acid having a mutation" that is selected from APC, DCC, NF1, NF2, RET, VHL, and WT-1 is detected in tissue from a lymph node that is "external to a primary neoplasm" and "appears histologically normal" as an indicator of metastases.

It is unpredictable as to whether one of skill in the relevant art could use the invention of the instant claims. The claims as written require that each of the target nucleic acids recited therein may be detected in tumor margins and lymph node tissues that are or appear "histologically normal/histologically normal upon examination." However, the specification only exemplifies the detection of a different target nucleic acid, p53, in surgical margins and lymph nodes that appear histologically normal by light microscopy in patients afflicted with head and neck squamous cell carcinoma (see Examples 1-4, as well as Figures 2-5 and 7-9). Applicant's specification does not

provide any evidence that mutated versions of any of the nucleic acids recited in the instant claims were -- or can be -- detected in any type of sample (from any type of patient, with any type of cancer) that is or that appears "histologically normal/histologically normal upon examination." Many types of microscopy were available for use by those of skill in the art at the time the invention was made, and additional techniques such as staining and labeling may be employed with microscopy to increase its sensitivity. Given the absence of evidence and data provided in the specification regarding the detection of the nucleic acids of the claims in any type of "histologically normal' sample, it is unpredictable as to whether said nucleic acids may in fact be detected by the methods of the claims in such samples. With further regard to claims 12 and 25 and claims dependent therefrom, it is further noted that the specification is also silent with regard to detection of any of these nucleic acids in any type of "histologically normal' sample as an indicator of metastasis. Lacking guidance from the specification, one of skill in the art may look to the teachings of the art for further guidance and enablement of a claimed invention. However, in the instant case, the prior art is also silent with respect to any teachings that mutant versions of any of the genes of the instant claims may be detected in, e.g., surgical margins or lymph nodes that are or appear "histologically normal." The closest prior art reference, Nees et al (Cancer Research 53(18):4189-4196 [9/1993]), discloses that mutated p53 nucleic acids were detected in tumor margin specimens obtained from patients with head and neck cancers (see, e.g., Table 3, p. 4191, 4193). However, Nees et al note that their findings with p53 suggest that multiple tumor development may be a "multifocal

polyclonal process" rather than a monoclonal process "initiated by lateral movement" of premalignant cells, and state that "At present, there is no information as to which other tumor suppressor genes" might be among those that (along with p53) undergo genetic changes contributing to head and neck cancer progression (see page 4195, last paragraph). Thus, the teachings of the prior art suggest the manner in which cells containing the mutant nucleic acids of the claims might arise in lymph nodes and/or tumor margin tissues was not clear at the time the invention was made. Further, the teachings of the specification also support a conclusion that p53 is not analogous or equivalent to the genes of the present claims; for example, page 11 of the specification teaches that p53 mutations are found in "50% of all cancers," while showing that the genes of the present claims are associated with particular cancer types. It is also again noted that Bilchik et al (previously cited by applicant) taught in 2001 (i.e., many years after applicant's effective filing date) that because different sections are employed for RT-PCR and histopathological analysis of samples, tumor cells may be present in one place and not in the other (page 1134, left column); thus, a skilled artisan would recognize that a single sample may include areas including tumor cells and areas lacking tumor cells, such that different findings may be obtained using the same sample. It is again noted that neither the specification nor the prior art exemplify the detection of any of the genes of the claims in any sample that has also been shown to be "histologically normal/histologically normal upon examination". Given the lack of evidence in both the specification and in the art with regard to how cells comprising the nucleic acids of the claims might come to be present in lymph nodes and/or tumor

margin tissues, it cannot be predicted whether specimens taken from these locations that were found to contain detectable levels of such target nucleic acids would in fact appear as what one of skill in the art would consider "histologically normal." As noted above, many types of microscopy were available for use by those of skill in the art at the time the invention was made, and additional techniques such as staining and labeling may be employed with microscopy to increase its sensitivity. While it is certainly possible that such specimens might be identified, this question could only be resolved by further experimentation. Given the high level of skill of one skilled in the relevant art, it is clearly within the ability of such an artisan to conduct such further experimentation – however, the outcome cannot be predicted, and it is in fact possible that no quantity of experimentation would be sufficient to enable the claims. As it is unknown as to whether any quantity of experimentation would actually be sufficient to enable the practice of the claimed invention, it would require an undue quantity of experimentation to use the invention of the instant claims.

The response of November 25, 2008 traverses the rejection on the following grounds.

The reply argues that the specification provides "abundant guidance for the practice of the claimed invention as well as a detailed working example," and that one of skill in the art "would have reasonable expected that mutations in any of the other recited tumor suppressor genes, which are found in the primary tumor, could similarly be detected in normal-appearing tissues into which tumor cells from the primary tumor had migrated." The reply urges that although the claimed invention had not been

reduced to practice, such reduction to practice was not required to enable the invention in the present case, as the guidance provided in the specification was sufficient. These arguments have been thoroughly considered but are not persuasive. It is acknowledged that enablement does not necessarily require reduction to practice of a claimed invention, and it is again acknowledged that applicant's specification is enabling with regard to non-claimed embodiments (i.e., p53). However, it is again noted that neither the teachings of the prior art nor those of the specification have established that p53 is analogous to the genes of the instant claims. Applicant's own specification discloses that p53 is associated with a wide variety of cancers while the genes of the claims are associated only with particular cancer types, emphasizing the differences that exist between p53 and the genes of the instant claims. Further, neither the specification nor the prior art provide any actual evidence that any of the genes encompassed by the instant claims had been or could be successfully detected in "histologically normal" samples at the time the instant invention was made (which is the date relevant to enablement of a claimed invention). The examiner has not disputed the fact that one could have successfully attempted such diagnostic techniques on histologically normal tissues using techniques known in the art and taught in the specification; however, enablement of the instant claims requires actual detection, not attempted detection. Further, the teachings of Nees et al referenced above indicate a lack of predictability and knowledge with respect to p53, and further do not support a conclusion that p53 is analogous to other genes such as those of the claims. While

applicant argues that this is the case, applicant has not provided, e.g., evidence or prior art references that actually support these arguments. As discussed in MPEP 2164.05:

> To overcome a *prima facie* case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure, as filed, would have enabled the claimed invention for one skilled in the art at the time of filing.

As applicant has not demonstrated by arguments and/or evidence that the invention claimed was enabled at the time of filing, this rejection is maintained.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 571/272-0744. The examiner can normally be reached on Monday and Thursday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571/272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Diana B. Johannsen/
Primary Examiner, Art Unit 1634